REMARKS

Claims 117-120 and 124-132 are pending in this application. Claims 130-132 have been withdrawn from prosecution as directed to non-elected subject matter. Claim 121-124 and 133-135 have been previously cancelled.

According to the Office Action of September 4, 2008, claims 117 and 118 have been objected to, and claims 117-120 and 124-129 have been rejected under 35 U.S.C. § 103(a). In view of the amendments to the claims and remarks below, Applicants respectfully request that the objections and rejections be reconsidered and withdrawn.

OBJECTION TO THE CLAIMS

Claims 117 and 118 have been objected to for containing typographical and/or grammatical errors. Applicants have amended these claims in accordance with the suggestions made by the Examiner in the Office Action. Accordingly, withdrawal of these objections is respectfully requested.

REJECTION UNDER 35 U.S.C. § 103

I. REJECTION OF CLAIMS 117-120 AND 124-126

Claims 117-120 and 124-126 have been rejected under 35 U.S.C. § 103 as unpatentable over Chakravorty[1] in view of Jaber[2]. Claims 127-129 have been rejected under 35 U.S.C. § 103 as unpatentable over Chakravorty in view of Jaber, U22037[3], Marchetti[4] and Buck[5]. Applicants respectfully traverse these rejections for the reasons set forth below.

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[1] Chakravorty *et al.*, "Novel use of guanidinium isothiocyanate in the isolation of *Mycobacterium tuberculosis* DNA from clinical material," FEMS MICROBIOLOGY LETTERS (2001) 205: 113-117 ("Chakravorty).

[2] Jaber *et al.*, "A simple method of DNA extraction from *Mycobacterium tuberculosis*," TUBERCLE AND LUNG DISEASE (1995) 76: 578-581 ("Jaber").

[3] GenBank Accession No. U22037 ("U22037").

[4] Marchetti *et al.*, "Evaluation of PCR in detection of *Mycobacterium tuberculosis* from formalin-fixed, paraffin-embedded tissues: comparison of four amplification assays," J. OF CLINICAL MICROBIOLOGY (1998) 36(6): 1512-1517 ("Marchetti").

[5] Buck *et al.*, ""Design strategies and performance of custom DNA sequencing primers," BIOTECHNIQUES (1999) 27(3): 528-536 ("Buck")

A. Recited Invention

This invention, as recited in amended claim 117, is an effective and economical method of processing clinical samples useful for simple, rapid, safe, and sensitive diagnosis of bacterial infections. The method recites six solutions:

- Solution 1: a Universal Sample Processing (USP) solution comprising 3-6 M Guanidinium Hydrochloride (GuHC1), 40-60 mM Tris-Cl at a pH ranging between 7.3-7.7, 20-30 mM EDTA, 0.3-0.8% Sarcosyl, and 0.1-0.3 M beta-mercaptoethanol;
- Solution 2: 65 to 70 mM sodium phosphate at pH ranging between 6.7 to 6.8, or sterile water;
- Solution 3: 0.03 to 0.08% of polysorbate 80;
- Solution A: 8-12% a chelating resin;
- Solution B: 0.02 to 0.04% polyoxyethylene phenyl ether; and
- Solution C: 0.2-0.4% polysorbate 20

The method comprises obtaining the clinical sample. The clinical sample is mixed with 1.5 to 2 volumes of Solution 1. The clinical sample and Solution 1 are homogenized in a manner that avoids frothing. Solution 2 is added to the homogenate followed by centrifugation to obtain a pellet. The pellet is washed with Solution 1 and then optionally washed with water. The pellet is respsended in one or more of Solutions 3, A, B and/or C to obtain a processed sample.

B. Cited References

Chakravorty discusses a DNA isolation method.[6] The method consists of homogenizing a tissue in 5M GITC, 50mM Tris-CL, pH 7.5, 25 mM EDTA 0.5% Sarcosyl, 0.2 M β-mercaptoethanol, which Chakravorty refers to as an "inhibitor removal solution" or "IRS".[7] As the Office Action acknowledges, Chakrovarty does not teach using GuHCl.

The Office Action contends that Chakrovarty section 2.2.1 adding sterile water to the homogenate because Chakrovarty's IRS inherently includes water. Assuming that

[6] Chakravorty at page 114.

[7] *Id.*

Chakrovarty's IRS inherently includes water, Chakrovarty does not separately teach to add water to a homogenate. At best, it teaches adding IRS and water to a clinical sample, not a homogenate.

According to Charkovarty's method, once homogenized, the sample is centrifuged and the supernatant discarded.[8] The pellet is resuspended in the IRS, centrifuged, and the subsequent pellet is rinsed with water and dried.[9]

Jaber is directed to a method of DNA extraction of *M. tuberculosis*.[10] Jaber's method consists of incubating a mycobacterium culture in a lysis buffer consisting of 6M guanidinium HCl, 50mM EDTA, 1 mM 2-mercaptoethanol and 0.05% Tween 80.[11] After the bacteria is incubated in the lysis buffer, the sample is centrifuge. The resulting supernatant transferred into a clean tube, and the DNA precipitated with cold ethanol.[12]

C. Argument

Applicants respectfully disagree that Chakoravorty teaches adding solution 2 to the homogenate, or that one would find it obvious to substitute GITC with GuHCl in view of these references. Taking Chakorvaorty as a whole, one would not reasonably conclude that solution 2 is added to the homogenate. Furthermore, the Office Action contends that Jaber teaches that "GuHCl was a chaotropic agent that use useful for cell lysis, inactivation of nucleases, dissociation of nucleoproteins and disturbance of cellular and subcellular structures (see page 579)."[13] Applicants respectfully disagree because Jaber teaches that GuHCl is useful in lysising mycobacterium, not tissue; and because the Office Action has not explained why one would simply substitute Charkovarty's GITC with Jaber's GuHCl as opposed to substituting Charkovarty's lysis buffer for Jaber's lysis buffer.

Point I. Chakrovarty section 2.2.1 does not teach a separate step of adding solution 2 to a homogenate.

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[8] *Id.*

[9] *Id.*

[10] Jaber at 578.

[11] *Id.* at 579.

[12] *Id.*

[13] Office Action at page 12.

When making a rejection under 35 U.S.C. § 103, the Examiner has the burden of establishing a *prima facie* case of obviousness. *In re Fritch*, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992). To establish this, each and every claimed element must be taught or made obvious by the applied references. *Ex parte Hellums*, Application No. 09/103,704, Appeal No. 2001-2694, 2003 WL 25281923 at *4 (BPAI Jul. 15, 2003); *Ex parte Likins*, Application No. 10/010,392, Appeal No. 2004-0760, 2004 WL 4981756 at *3 (BPAI Apr. 8, 2004).

The Office Action contends that Chakrovarty teaches adding a second solution to the homogenate because solution 1 inhererntly includes water by citing Chakrovarty section 2.2.1. This section of Chakrovarty states:

> Mince and homogenize tissue in 5 M GITC, 50mM Tris-Cl, pH 7.5, 25 mM EDTA, 0.5% Sarcosyl, 0.2 M β-mercaptoethanol (inhibitor removale solution, IRS) in a mini bead beater (Biospec, USA) using 1-mm glass beads for 30-60 s. Centrifuge at 600 x g for 3 min. Centrifuge the supernatant at high speed and discard supernatant.

In contrast, claim 117 recites "... mixing 1.5 to 2 volumes of Solution 1 with the sample, homogenizing the mixing while avoiding frothing, adding Solution 2 to the homogenate followed by centrifugation to obtain a pellet ...." Thus, it recites that solution 1 is added to the sample. The sample and solution 1 are homogenized. After the sample is homogenized, solution 2 is added to the homogenate. Even assuming that a fair reading of Chakrovarty would include a teaching of solution 2 (i.e. sterile water), it does not teach adding sterile water in a separate step.

Moreover, a fair reading of Chakrovarty does not include that sterile water, instead of IRS, can be used. To establish a *prima facie* case of obviousness, the prior art must be evaluated based on what it, *as a whole*, teaches to one of ordinary skill in the art. *In re McLaughlin*, 443 F.2d 1392 (CCPA 1971). Here, Chakrovarty, as a whole, teaches that the IRS is not sterile water. Even assuming that IRS comprises sterile water, for the purposes for a rejection under Section 103, a fair reading of Chakrovarty, as a whole, would not prompt one of ordinary skill to conclude that sterile water can be used instead of Chakrovarty's IRS. Nor would one of ordinary skill in the art reasonably expect that Chakrovarty's DNA isolation method would work if Chakrovarty's IRS was substituted with sterile water.

Accordingly, Chakrovarty does not suggest adding solution 2 to a homogenate, nor does it suggest solution 2 in and of itself.

Point II. The Office Action has not provided a reason why one would substitute Chakrovarty's GITC for Jaber's GuHCl when Jaber only teaches lysing mycobacterium, not tissue.

There is no reason to expect that Chakrovarty's GITC can be substituted with Jaber's GuHCl when isolating DNA from tissue according to Chakrovarty's method because Jaber's GuHCl was only disclosed as being useful in isolating DNA from bacteria, which requires less stringent conditions that isolating DNA from tissue. When making a rejection under 35 U.S.C. § 103, the Examiner has the burden of establishing a *prima facie* case of obviousness. *In re Fritch*, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992). To establish a *prima facie* case of obviousness, the prior art must be evaluated based on what it, as a whole, teaches to one of ordinary skill in the art. *In re McLaughlin*, 443 F.2d 1392 (CCPA 1971).

As part of a *prima facie* case, an examiner must establish some reason to combine the references. *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1731 (2007); *Takeda Chemical Industries, Ltd. v. Alpharpharm Pty., Ltd.*, 492 F.3d 1350, 1356-1357 (Fed. Cir. 2007). The *KSR Int'l* Court acknowledged the importance of identifying a reason that would have prompted a person of ordinary skill in the art to combine the elements in the way the claimed invention does. *KSR Int'l*, 127 S.Ct. at 1731; *Takeda Chemical*, 492 F.3d at 1356-1357. Repeatedly throughout the *KSR Int'l* decision, the Court discussed the importance that the result obtained by a particular combination was predictable to one of ordinary skill in the art. *KSR Int'l*, 127 S.Ct. at 1731 and 1739-1742.

Chakrovarty teaches lysing tissue with a lysis buffer comprising GITC, whereas Jaber teaches lysing a bacteria with GuHCl. There are also more differences than just GITC and GuHCl between Chakrovarty's and Jaber's lysis buffers. There is no explanation why one would reasonably expect GuHCl to lyse a tissue when Jaber only teaches lysing bacteria, and there is no explanation why one would reasonably expect GuHCl to work in Chakrovarty's formulation.

Jaber discloses to a protocol using GuHCl for extracting DNA from mycobacterium. In contrast, Chakravorty discloses a protocol using GITC for extracting

DNA from tissue. Thus, in order for the references to be properly combined, there must be some reason why one would reasonably expect that GuHCl would be equally as useful in extracting DNA from tissue as from bacteria.

There are considerable biochemical differences between tissue and bacteria. Tissue contains multiple cells interconnected by proteins such as cell adhesion molecules, and the nuclei, which house the DNA and provide a further obstacle to isolating DNA. Bacteria, on the other hand, do not have the level of interconnection exhibited in tissue cells, and do not have nuclei. These differences, among others, are the reason for using more stringent conditions to isolate DNA from tissue, as opposed to bacteria.

Jaber states that GuHCL "inactives both RNase and DNase, dissociates nucleoproteins, and distrurbs cellular and subcellular structure, and its pH and ionic strength favour the native form of the DNA."[14] However, it continues to state that "[t]he effect of this solvent and the thermal degradation of the cellular organic material, combined with further protein denaturation by phenol and chloroform, have resulted in the isolation of biologically active and completely intact DNA from *M. tuberculosis* ...,"[15] not tissue. Moreover, this latter passage suggests that GuHCl may not be stringent enough to denature enough proteins to isolate DNA from tissue.

Thus, Jaber does not suggest that GuHCl is useful in isolating DNA from tissue, and the Office Action does not provide the requisite reason why one would reasonably expect that GuHCl would be useful in Chakrovarty's application. Accordingly, a *prima facie* case of obviousness has not been established.

Point III. The Office Action has not explained why one would combine the two references when the DNA sample in Chakravorty is isolated by high speed centrifugation while the DNA in Jaber is isolated by precipitation.

According to Jaber, once the bacteria is lysed, the sample is centrifuged at 10,000 g at 4°C for ten minutes. The resulting supernatant is thereafter transferred to a clean tube, and the DNA is precipitated with ice cold ethanol. According to Jaber, the ethanol

[14] Jaber at pate 579.

[15] Id.

precipitation step is crucial.[16] In contrast, Chakrovarty discloses a method of homogenizing tissue. The homongenate is centrifuged at 600 g for three minutes. The resulting supernatant is centrifuged at high speed, which results in the pelleting of the desired DNA sample.

In view of these differences in procedure, the Patent Office should explain why one would expect, nevertheless, that a DNA sample that is pure enough for PCR amplification can be obtained when using GuHCl. Without such an explanation, a *prima facie* case of obviousness has not been established.

Point IV. The Office Action has not explained why one would pick only GITC for GuHCl as opposed to substitute Jaber's entire lysis buffer formulation for Chakrovarty's lysis buffer.

Moreover, there is no reason provided why one would take Jaber's GuHCl, instead of Jaber's entire lysis buffer. The lysis buffers taught by the individual references are different from each other; therefore, it is not as simple as substituting the GITC in Chakrovarty's buffer for the GuHCl used in Jaber's buffer (see Table 1). Specifically, Jaber discloses using GuHCL and Tween 80, which are not used in Chakrovarty's lysis buffer. Furthermore, Jaber and Chakrovarty have different concentrations of EDTA and 2-mercaptoethanol.

Table 1: Side-by-Side Comparison of Lysis Buffers

Compound	Chakrovarty	Jaber	Recited Solution 1
GuHCL	0	6 M	3-6 M
GITC	5 M	0	
EDTA	25 mM	50 mM	20-30 mM
Tris-Cl	50 mM	0	40-60 mM
2-mercaptoethanol	0.2 M	1 mM	0.1-0.3 M
Sarcosyl	0.5 %	0	0.3-0.8 %
Tween 80	0	0.05 %	

In order to establish a *prima facie* case of obviousness, the references as a whole must be evaluated. Jaber does not commoditize GuHCl into an interchangeable part that can be used in other lysis buffers. Nor does Chakrovarty declare that GITC can be easily substituted for some other compound. There is no reason why one would believe that Jaber's GuHCl would be equally as effective in a lysis buffer without Tween 80, with half as much

[16] Jaber at 579.

EDTA, or with 50 times less 2-mercaptoethanol. Without such a reason, a rejection under Section 103 cannot be maintained.

Furthermore, Jaber expressly states that phenol and chloroform are necessary to isolate intact DNA.[17] Chakrovarty does not require these compounds. Thus, without some reason why one would expect GuHCl to be effective without phenol or chloroform, there is no reason why one would combine Chakrovarty and Jaber. Accordingly, a *prima facie* case of obviousness has not been established.

II. REJECTION OF CLAIMS 127-129

Claims 127-129 have been rejected under 35 U.S.C. § 103 as unpatentable over Chakravorty in view of Jaber, Nair, U22037, Marchetti and Buck. Claims 127-129, which ultimately depend from claim 117, are patentable over these references for the same reason claim 117 is patentable over the combination of Chakravorty, Jaber and Nair

Additionally, there is no motivation to combine these references. According to *Yamanouchi Pharmaceutical*, there must be some motivation for a hypothetical person of ordinary skill in the field at the time of the patent to take the myriad components of various teachings of prior art and combine them to create the claimed invention. *Yamanouchi Pharmaceutical Co. v. Danbury Pharmacal, Inc.*, 21 F.Supp.2d 366, 373, 48 U.S.P.Q.2d 1741 (S.D.N.Y. 1998), *aff'd*, 231 F.3d 1339 (Fed. Cir. 2000), *reh'g and reh'g en banc denied by*, 2000 U.S. App. LEXIS 34047 (Fed. Cir. 2000). In *Yamanouchi Pharmaceutical*, the court found that a skilled artisan would not be motivated to dispel all potential compounds disclosed in the cited reference, particularly when many of the disclosed compounds did not ever enter clinical trials due to insufficient potency, side effects or toxicity. *Id.*

Likewise, there is no motivation to pick over the vast number of possible primers to arrive at the particularly claimed primers. Without such a motivation, the references cannot be combined.

[17] Jaber at 579.

CONCLUSION

Accordingly, claim 117 is patentable over the cited references. Claims 118-120 and 124-129 are also patentable over the cited references by virtue of their dependence on claim 117. Therefore, in view of the amendments to the claims and remarks, Applicants respectfully request that the objections and rejections asserted in the Office Action of September 4, 2008 be reconsidered and withdrawn, that pending claims 117-120 and 124-129 be allowed. The Applicants further request that claims 130-132 be rejoined and allowed.

Respectfully submitted,

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